Reviewer's report

Title: Exploratory trials, confirmatory observations

Version: 1 Date: 21 November 2010

Reviewer: Robyn Bluhm

Reviewer's report:

This paper critiques the claim that RCTs are the best method for providing evidence upon which to base clinical decisions. The author argues that a patient centered approach to treatment requires the development of a new clinical research method that reflects the paradigm of personalized medicine. The paper begins with a critique of RCTs, then describes the new approach that the author suggests as an improvement of current practice. This new approach can be divided into two phases. Prior to the authorization (approval?) of a new therapy, RCTs should be conducted. Yet these should not be the “mega trials” that are currently conducted. Instead a series of small trials should be performed in which diverse populations are targeted on the basis of particular characteristics of interest. (The participants in each individual trial should be homogenous, but the trials should target different populations.) In the second, post-approval phase, observations should be made systematically, with the goal of finding exceptions to the claim that the drug is safe and effective. The author suggests that electronic health records could be a helpful tool in this phase of research.

Major Compulsory Revisions

1. The overall argument presented in this paper is promising, but needs a great deal of work to be adequately developed and clarified. Given the length of the paper, the first section (the criticism of RCTs) could be shortened a great deal by referring to the sizable literature on this topic. (See, for example, the references at the end of this review.) This would give the author more room to develop his positive recommendations. For example, it is not clear what (epistemic or practical) advantages would be gained from conducting small RCTs in narrowly defined populations versus conducting a larger trial and looking for variation in subgroups defined in the same way.

2. Similarly, the recommendations for post-approval studies should be better developed. In some sections of the paper (e.g. page 5’s recommendation that trust in clinical observation is important and p. 4’s discussion of the idea of providing definitive evidence for individual patients) the author seems to be recommending more careful monitoring of individual patients by clinicians. Elsewhere (e.g. the talk of the “average level” on page 6 and section on electronic patient records), the author seems to be advocating more research at the population level. Although these recommendations are not incompatible, they are different and so the paper should be careful to distinguish between them.
3. The author also needs to clarify what is meant by “personalized medicine.” In some parts of the paper, this seems to just be related to patient centered medicine, but in others it appears to be being identified with pharmacogenomics.

4. The second describing RCTs as inductive reasoning needs to be reworked. RCTs are generally viewed as being a hypothetico-deductive method (though see the Cartwright article cited below), so some argument for the author’s non-standard position is necessary.

Discretionary Revisions

1. The author mentions N=1 trials as a good example of individualized medicine; however, these trials are only applicable in limited circumstances. How would “formal case studies” be more helpful or more broadly applicable than N=1 trials?

Papers discussing RCTs and their role in clinical research


Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.